REMARKS

The Invention

The invention provides a diagnostic method in which the degree of methylation within the promoter region and the 5' end of the coding sequence of the HIN-1 gene in a test cell is determined. A high degree of methylation is an indication that the test cell is a cancer cell.

Status of the claims

Claims 1-34 are pending and claims 23 and 24 are under consideration in this application, claims 1-22 and 25-34 having been withdrawn from consideration as allegedly being drawn to separate inventions. Claims 23 and 24 stand rejected. After entry of the above amendments, claims 23-46 will be pending and claims 23, 24, and 35-46 will be under consideration, claims 1-22 having been cancelled and new claims 35-46 added.

New claims 36-43 and the amendments to claim 23 are supported by the specification, e.g., at page 26, lines 11-19; page 27, line 26, to page 28, line 15; Example 4; and the Sequence Listing. New claims 35 and 44 are supported by the specification, e.g., at page 26, lines 21-24. New claims 45 and 46 are supported by the specification, e.g., at page 30, line 29, to page 31, line 24, and Example 4. No new matter has been added.

Amendment to the Specification

As requested on page 2, lines 10-12, of the Office Action, Applicants have deleted the hyperlink on page 14, lines 19-20, of the application (see the amendment to the specification above).

Substitute Sequence Listing

Applicants submit herewith a substitute hard copy and a substitute computer readable form of the Sequence Listing. By comparison with the nucleotide sequence (SEQ ID NO:19) shown in Fig. 8, it can be seen that in the original Sequence Listing the sequence designated SEQ ID NO:19 is incorrect while that in the enclosed substitute Sequence Listing is correct. Please replace the Sequence Listing currently in the application with the enclosed substitute Sequence Listing. No new matter is added by this substitution.

35 U.S.C. § 112, second paragraph, rejection

Claims 23-24 stand rejected as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. Applicants respectfully traverse this rejection.

From the comments on page 3, lines 4-9, of the Office Action, Applicants understand the Examiner's position to be that the term "HIN-1 promoter region" would not clearly appraise one of skill in the art of what gene the specified promoter region was a part, and thus such a person would not be able to tell whether the HIN-1 gene referred to in the instant claims is the same or different from another gene given the same name. Applicants disagree with this position.

The specification discloses full-length cDNA sequences corresponding to human and mouse HIN-1 genes (SEQ ID NOs: 3 and 7, respectively; Figs. 1A and 3A) and all but a small part of the 5' end of leader sequence of a cDNA corresponding to the rat HIN-1 gene (SEQ ID NO: 20; Fig. 9A). The protein encoded by the human gene is 60.8% homologous to that encoded by the mouse gene and the 62% homologous to that encoded by the rat gene; the rat HIN-1 protein is 84% homologous to the mouse HIN-protein (see Example 2). The mouse and human HIN-1 proteins, at least, are the same length (i.e., 104 amino acids) and it seems likely that the rat protein has the same, or a very close, length (e.g., Example 2). From this information in the specification, the description of HIN-1 gene expression patterns in various normal and malignant tissues (e.g., Example 3), and the depiction of part of the human HIN-1 promoter region (SEQ ID NO:19; Fig. 8), one of skill in the art would readily be able to discriminate, or establish the identity between, a HIN-1 gene of the instant application, and any other gene hypothetically and coincidentally also designated HIN-1.

In light of the above considerations, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 102(b) rejection

Claims 23-24 stand rejected as allegedly being anticipated by Baylin et al. (U.S. Patent No. 5,922,590; the "'590 patent"). Applicants respectfully traverse this rejection.

From the comments on page 4, lines 1-6, of the Office Action, Applicants understand the Examiner's position to be that, insofar as the term "HIN-1 promoter region" is indefinite, it covers "any polynucleotide sequence" and hence the instant claims are anticipated by the '590 patent that discloses a method of analyzing methylation of what the Examiner says is a "HIN-1" gene. Applicants disagree with this position.

First, as argued above, given the teachings of the instant specification, the term "promoter region of the HIN-1 gene" in claim 23, as amended, is not indefinite. The HIN-1 gene is clearly described in the specification such that one of ordinary skill would immediately understand whether a given gene is or isn't an HIN-1 gene. Second, the HIN-1 promoter region of the claims can readily be distinguished from the promoter region disclosed in the '590 patent. The promoter region analyzed in the '590 patent is not of a gene designated **HIN-1**, but rather of a gene designated **HIC-1** (see, e.g., Abstract). "HIN-1" stands for "High In Normal 1" (specification at page 1, lines 16-17), while "HIC-1" stands for "Hypermethylated In Cancer-1" ('590 patent at col. 4, line 43). The HIC-1 protein is 547 amino acids in length (see, e.g., the Sequence Listing of the '590 patent), while the human HIN-1 polypeptide is 104 amino acids long (see above). Neither the HIC-1 polypeptide (SEQ ID NO:3 of the '590 patent) nor the cDNA encoding it (SEQ ID NO:1 of the '590 patent) has significant homology to the human HIN-1 polypeptide (SEQ ID NO: 1 of the instant application) or the cDNA encoding it (SEQ ID NO:3 of the instant application), respectively. Moreover, while there is some overlap in the range of tissues in which the two genes are expressed (see Example 3 and Figs. 5A and B of the instant application and Example 4 and Figs. 3 and 4 of the '590 patent), there are clear differences: for example, while HIN-1 is apparently not detectably expressed in thymus, ovary, or small intestine, HIC-1 is strongly expressed in these tissues. Finally, while the HIN-1 protein is a growth-inhibitory cytokine (see, e.g., Example 5 of the instant application), the HIC-1 protein is predicted to be a transcription factor (see, e.g., column 24, lines 26-29, of the '590 patent).

In view of all these factors, it is clear that the HIC-1 and HIN-1 genes are not the same genes and hence that the HIC-1 and HIN-1 promoter regions are not the same promoter regions. Thus, the present claims are not anticipated by the '590 patent. Applicants therefore respectfully request that the rejection under 35 U.S.C. §102(b) be withdrawn.

CONCLUSION

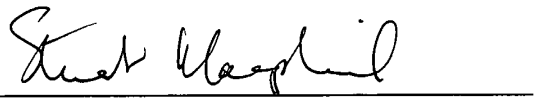
In summary, for the reasons set forth above, Applicants maintain that the pending claims patentably define the invention. Applicants request that the Examiner reconsider the rejections as set forth in the Office Action, and permit the pending claims to pass to allowance.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicants' undersigned representative can be reached at the telephone number listed above.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 00530-094001.

Respectfully submitted,

Date: 8/28/03



Stuart Macphail, Ph.D.
Reg. No. 44,217

Fish & Richardson P.C.
45 Rockefeller Plaza, Suite 2800
New York, New York 10111
Telephone: (212) 765-5070
Facsimile: (212) 258-2291

20682774.doc